

POSTER PRESENTATION

Open Access

Circulating and tumor-based biomarkers predict clinical activity in cancer patients treated with the engineered anti-PD-L1 antibody MPDL3280A

Marcin Kowanetz^{1*}, Christina Rabe², Yuanyuan Xiao¹, Qun J Wu¹, Hartmut Koeppen¹, Cecilia Leddy¹, Rajesh D Patel¹, John Powderly³, Holbrook Kohrt⁴, Scott Gettinger⁵, Jean-Charles Soria⁶, Roy S Herbst⁷, Rupal Desai¹, Mitchell Denker¹, Jane Ruppel¹, Marigold Boe¹, Rin Nakamura¹, Ling Fu¹, Teiko Sumiyoshi¹, Ahmad Mokatrini¹, Xiaodong Shen¹, Gregg Fine¹, Daniel S Chen¹, Priti S Hegde¹

From Society for Immunotherapy of Cancer 29th Annual Meeting
National Harbor, MD, USA. 6-9 November 2014

PD-L1 expressed in the tumor microenvironment regulates Th1 immune responses and mediates cancer immune evasion through interactions with PD-1 or B7.1 receptors on activated T cells. MPDL3280A, an engineered human monoclonal antibody, targets PD-L1 and inhibits its function. To identify immunologic predictive and pharmacodynamic biomarkers of MPDL3280A treatment, we performed a comprehensive analysis of tumors and blood samples collected at baseline and/or on treatment from ~280 patients with locally advanced or metastatic solid tumors, including NSCLC, RCC, melanoma and bladder cancer. Regardless of tumor type, clinical responses were characterized by PD-L1 expression, the presence of markers of T cell activation (Th1 gene signature and CTLA4), and the absence of fractalkine at baseline in the tumor microenvironment. Elevated baseline expression of IFN- γ and IFN- γ -inducible genes (e.g., *IDO1* and *CXCL9*) was associated with MPDL3280A response in melanoma but not NSCLC or RCC. On treatment, responding tumors showed increased infiltration of Th1-dominant immune infiltrate and evidence of adaptive PD-L1 up-regulation. In contrast, progressing tumors displayed the following patterns of tumor-infiltrating lymphocytes (TILs) and PD-L1 expression: (1) few/no TILs and absent PD-L1 expression (immunologic ignorance), (2) TILs present with minimal/no PD-L1 expression (non-functional immune responses), or (3) TILs residing solely around the tumor cell mass outer edge (excluded infiltrate), suggesting that resistance to

MPDL3280A may be associated with impaired T cell trafficking and/or function.

Profiling of ~180 circulating biomarkers revealed that plasma concentrations of IL-18 and interferon-inducible T cell alpha chemoattractant (ITAC) increased in all patients following MPDL3280A treatment, representing a pharmacodynamic measurement of PD-L1 inhibition. In addition, analysis of PBMC showed an increase in T cell activation, as measured by IFN- γ and granzymes A and B gene expression in responders following MPDL3280A treatment, consistent with the observations in responding tumors. Baseline soluble PD-L1 was not associated with response. Some indication-specific biomarkers, such as plasma VEGF, decreased in responders with RCC but not with other indications. In NSCLC, a decrease in tumor burden markers, CA-125 and CEA, was associated with response. Similarly, IL-6 and IL-8 were differentially expressed on treatment in responders vs non-responders. Additionally, responders exhibited a decrease in circulating tumor DNA (ctDNA) in plasma, suggesting that ctDNA may be used to monitor MPDL3280A clinical activity in NSCLC.

In conclusion, these data provide general and indication-specific mechanistic insights into immune checkpoint inhibition, potential mechanisms of response and resistance, as well as identification of potential predictive and pharmacodynamic biomarkers of anti-PD-L1/PD-1 clinical activity across multiple tumor types.

Authors' details

¹Genentech, Inc., USA. ²Roche Diagnostics GmbH, Germany. ³Carolina BioOncology Institute, NC, USA. ⁴Stanford University, Stanford, CA, USA. ⁵Yale

¹Genentech, Inc., USA

Full list of author information is available at the end of the article

University, New Haven, CT, USA. ⁶Gustave Roussy, Villejuif, France. ⁷Yale School of Medicine, New Haven, CT, USA.

Published: 6 November 2014

doi:10.1186/2051-1426-2-S3-P136

Cite this article as: Kowanetz *et al.*: Circulating and tumor-based biomarkers predict clinical activity in cancer patients treated with the engineered anti-PD-L1 antibody MPDL3280A. *Journal for ImmunoTherapy of Cancer* 2014 **2**(Suppl 3):P136.

**Submit your next manuscript to BioMed Central
and take full advantage of:**

- Convenient online submission
- Thorough peer review
- No space constraints or color figure charges
- Immediate publication on acceptance
- Inclusion in PubMed, CAS, Scopus and Google Scholar
- Research which is freely available for redistribution

Submit your manuscript at
www.biomedcentral.com/submit

